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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/016,743	01/30/98	ROSENBLATT J	176/60192(UR

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EXAMINER	
HELMS,L	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/016,743	Applicant(s) Rosenblatt et al
	Examiner Larry R. Helms Ph.D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *16 Aug 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-76* is/are pending in the applicat

Of the above, claim(s) *11-24 and 26-76* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10 and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☒ The proposed drawing correction, filed on *16 Aug 2000* is ☒ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-76 are pending.

Claims 1-2 and 6 have been amended.

Claims 11-24 and 26-76 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

Claims 1-10 and 25 are under examination.

2. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.

3. The following Office Action contains some NEW GROUNDS of rejections.

Drawings

4. The proposed drawing correction and formal drawings, filed on 8/18/2000 have been approved by the draftsperson.

Rejections Withdrawn

5. The rejection of claims 1-10 and 25 under 35 U.S.C. 112, second paragraph, in the previous Office Action of paragraph 9A-C, as being indefinite for failing to particularly point out

and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims and arguments.

6. The rejection of claims 1-2, 5-6, 8, 10, and 25 under 35 U.S.C. 102(a) as being anticipated by Holzer et al (Cytokine 8:214-221, March 1996) is withdrawn in view of the amendments to the claims.

7. The rejection of claims 1-2, 5-8, 10, and 25 under 35 U.S.C. 102(e) as being anticipated by Holzer et al et al (U.S. Patent 5,824,782, filed 9/15/95) is withdrawn in view of the amendments to the claims.

8. The rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) and further in view of Bacus (U.S. Patent 5,514,554, filed 10/7/93) is withdrawn in view of the amendments to the claims.

Response to Arguments

9. The rejection of claims 1-10 and 25 under 35 U.S.C. 112, second paragraph, in the previous Office Action of paragraph 9d, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

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The response has been carefully considered but is deemed not to be persuasive. The response states that "chemokine or active fragment" are proteins that act as potent chemoattractants and are involved in the migration of inflammatory cells. In response to this argument Janeway et al (Immunobiology, The Immune System in Health and Disease, Current

Biology Limited, page 916-9-17, 1994) also states that chemokines function mainly as chemoattractants (9-16), however, Janeway et al also states "Why there are so many chemokines, and the exact role of each one in host defense and in pathological responses is not known." (Page 9-17). Thus, one skilled in the art would not know what a "chemokine active fragment" was if one does not know the exact role of the chemokine.

10. The rejection of claims 1-10, and 25 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric molecule comprising a binding domain which is an antibody or fragment thereof which specifically binds to the tumor associated antigen and a chemokine, does not reasonably provide enablement for a chimeric molecule comprising any binding domain and a chemokine active fragment because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained.

The response has been carefully considered but is deemed to not be persuasive. The response states "Ligands which bind to tumor cell associated antigens are well known to those of ordinary skill in the art." The response continues with an example from Bacus of gp39 and NDF. In response to this argument, it may be true that other ligands are known but one skilled in the art would not know from the disclosure alone how to produce chimeric molecules as broadly claimed. The specification fails to enable binding domains other than antibodies or antigen binding fragments and chemokine active fragments which are coupled to each other. As cited in

the previous Office action the references of Burgess et al , Lazar et al, Schwartz et al, and Lin et al were cited for the unpredictability in the art of protein chemistry in that replacement of amino acid residues can affect the biological activity. None of these references were addressed in the Office action. It is not enough to know that there may be other non antibody ligands which could be coupled to the chemokine, the specification needs to enable such molecules. It is well known in the art to couple antibodies through specific residues and regions to other proteins, however, it would require undue experimentation from the disclosure alone to practice the broadly claimed invention. Amending the claims by moving claim 2 into independent claim 1 and removing the term "or active fragment thereof" would be sufficient to obviate this rejection.

11. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) and further in view of Huston et al (Meth. Enzymol. 203:46-88, 1991) is maintained.

The response of 8/18/2000 has been carefully considered but is deemed not to be persuasive. The response states that Huston does not overcome the above-noted deficiencies of the Holzer et al patent. The response states that the Holzer patent does not suggest coupling the chemokine to the N terminus of the binding domain. In response to the arguments, it is true that Holzer does not teach coupling to the N terminus of the binding domain. This deficiency is made up for in the teachings of Huston. As stated in the previous Office Action Huston et al teach Fusion proteins with the effector fused at the amino terminal of the heavy chain of the antibody

(see pages 55-59 and Figure 3A). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds to a tumor cell associated antigen and a chemokine fusion as taught by Holzer et al with the chemokine linked to the amino terminus of the heavy chain as taught by Huston et al.

The following are some NEW GROUNDS of rejections

12. Claims 1-10 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-25 and 32-38 are indefinite for reciting "having an N terminus" in claim 1 because the exact meaning of the phrase is not clear. It is not clear how a binding domain, which in the claims does not have to be a protein, can have an N terminal. In addition, if the binding domain is a protein, what defines the "N terminal". Is a protein that has an N terminal methionine processed off not included in the claims?

13. Claims 1-8, 10, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) as applied to claims 1-4 above, and further in view of Huston et al (Meth. Enzymol. 203:46-88, 1991).

a. The claims recite a chimeric molecule comprising a binding domain and a chemokine which is coupled to the N terminus of the binding domain, wherein the binding domain is an antibody which binds a tumor cell associated antigen, wherein the chemokine is linked to the amino terminus of the heavy chain, further comprising a flexible linker, further the chemokine is IL-8 or RANTES, and compositions comprising such.

b. Holzer et al teach a fusion protein comprising an antibody to the EGF receptor, which is a tumor cell surface antigen expressed on breast cancer cells, (see abstract and column 1, lines 1-15) and the chemokine IL-8 that retains its activity (see column 6, lines 52-59). The construct comprises the antibody and a linker connecting the domains (see column 4, lines 55-56) and compositions of the chimeric molecules in PBS (see column 5, line 25, and column 8, lines 49-50). Holzer et al also teach the chemokine RANTES (see column 2, lines 37-40). The recitation of the intended use of "stimulating a tumor specific immuno response" is given no patentable weight in this rejection. Holzer et al does not teach a fusion protein comprising the chemokine linked to the N terminus of the antibody. This deficiency is made up for in the teachings of Huston et al.

c. Huston et al teach Fusion proteins with the effector fused at the amino terminal of the heavy chain of the antibody (see pages 55-59 and Figure 3A).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds to a tumor cell associated antigen and a chemokine fusion as taught by Holzer

et al with the chemokine linked to the amino terminus of the heavy chain as taught by Huston et al.

e. One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Huston et al teach "sFv analogs suggested that VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion" (see page 57, first full paragraph).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Huston et al teach "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv." (See page 57, second full paragraph).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huston et al (Meth. Enzymol. 203:46-88, 1991), and further in view of Bacus (U.S. Patent 5,514,554, filed 10/7/93) and Holzer et al (U. S. Patent 5,824,728, filed 9/15/95).

a. Amended claim 1 has been described supra. Claim 9 recites where in the binding domain specifically binds her2/neu.

b. Huston et al has been described supra. Huston et al does not teach a binding domain specific for her2/neu. This deficiency is made up for in the teachings of Bacus.

c. Bacus teach monoclonal antibodies to her2/neu.

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds her2/neu as taught by Bacus and a chemokine as taught by Holzer et al and couple the chemokine and the antibody by the N terminus as taught by Huston et al.

e. One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Bacus teach the antibodies to her2/neu can be used alone or linked to conjugates which can be used as therapeutic agents (see column 4,

lines 10-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Huston et al teach "sFv analogs suggested that VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion" (see page 57, first full paragraph).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Bacus teach the antibodies of the present invention are specific for the her2/neu product and significantly inhibit the tumorigenic growth of her2 cells. (See column 3, lines 59-67). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Huston et al teach "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv." (See page 57, second full paragraph).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The

examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Sheela G. Huff

SHEELA HUFF
PRIMARY EXAMINER

Respectfully,

Larry R. Helms Ph.D.

703-306-5879